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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,013	12/08/2005	Sharon Davis Boggs	PR60251USW	1077

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,013	BOGGS ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,28 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,26 and 38-40* is/are rejected.

7)☒ Claim(s) *2-25 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/08/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26, 28 & 38-40 are pending in the instant application, of which: **Claims 12, 28, 38 & 39** are currently amended. **Claims 27 & 29-37** are cancelled.

Priority

This application is a 371 of PCT/US04/17660, filed on 06/07/2004. Acknowledgement is made of Applicants' claim for benefit of US Provisional Patent Applications 60/477,251, filed on 06/10/2003, and 60/497,823, filed 08/26/2003. Said claim has been made in the oath and/or in the first paragraph of the Specification.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 12/08/2005 has been considered. Please refer to Applicants' copy of the 1449 submitted herein. NOTE: IDS documents with a line crossed through them have not been provided.

Allowable Subject Matter

The compounds according to formula (I) are free of the prior art; nothing known in the art anticipates or renders the compounds of the instant application obvious. The closest prior art related to the formula I is compound RN 859084-79-0, taught by Muth *et al.* (DE 507797, 03/14/1927). Compound RN 859084-79-0 is a carbazole derivative, meaning that all three rings in the tri-cyclo ring system are aromatic. This is

distinguishable from the compounds according to formula (I), which contain a partially saturated ring, making them tetrahydrocarbazoles.

Claim Rejections - 35 USC § 112, 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims recites a compound of formula (I) that further comprising a compound of formula (I) and the scope of this term is unclear, such that it fails to define the metes and bounds of its limitation. Perhaps it was intended for the claim to read, "The compound of formula (I) in claim 1 wherein R^6...; and R^7 is..." however, it is unclear. A compound cannot further comprise another compound (a composition is a mixture of two or more compounds. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 & 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein **X = NH or O**, does not reasonably provide enablement for compounds wherein **X = $S(O)_m$ (Claim 1)**.

Furthermore, while being enabling for salts and solvates for the compounds of formula (I), the specification does not reasonably provide enablement for "physiological functional derivatives thereof," **(Claims 1 & 26)**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) *The breadth of the claims;*
(B) *The nature of the invention;*
(C) *The state of the prior art;*
(D) *The level of one of ordinary skill;*
(E) *The level of predictability in the art;*
(F) *The amount of direction provided by the inventor;*
(G) *The existence of working examples; and*
(H) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The breadth of the claims - The nature of the invention

Claim 1 is drawn to tetrahydrocarbazoles according to formula (I), wherein the definitions of **R**, **X**, **A**, **R^1**, **n, p & q** are defined therein. Compounds according to formula (I) are useful as pharmaceuticals. Furthermore, pharmaceutically acceptable

salts, solvates, and physiological functional derivatives thereof are encompassed by this claim (and **Claim 26**).

The state of the prior art

A review of the literature provided by Applicant in the Information Disclosure Statement (IDS) and the CAS structure search results suggests that the state of the prior art is more advanced for species in which **X = NH or O**, whereas no species have been described wherein **X = $S(O)_m$**.

With respect to pharmaceutically acceptable salts, solvates, and physiological functional derivatives thereof, the state of the art is more advanced for solvates and salts, than it is for "physiological functional derivatives." Said term includes esters, amides, and prodrugs (specification, page 14). Esters and amides are indicative of the chemical design, however these examples do not limit the term. Prodrugs are included in this broad term. The state of the prior art is that prodrugs are an inactive form of a drug that exerts its effects after metabolic processes within the body converts it to a usable or active form. In other words, a prodrug is a drug that must be activated before it can produce a physiological effect. Prodrugs are designed to be appended to a particular functional group such as a carboxylic acid, alcohol, amine, phosphate, or phosphonic acid. Research is required to match the prodrug with the particular drug to overcome challenges including stability, rate of systemic prodrug cleavage, and safety. Furthermore, it needs to be decided what enzyme system is wanted to cleave the prodrug followed by the evaluation of the prodrug analogs in assays to measure

progress in achieving the desired properties (stability, solubility, cleavage of prodrug in biological matrices, pharmacokinetics in animal models, efficacy in animal models, and safety in animal models). This process is exactly like the process used to discover the active drug. The difficulty of discovering effective prodrugs is often underestimated and for all of the aforementioned reasons, the claimed invention is highly unpredictable.

The level of predictability in the art

The synthesis of complex natural products is an integral part of modern organic chemistry, however, even the synthesis of molecules or molecular fragments containing ten carbons or less can also pose great challenges. Examination of many synthetic endeavors, large and small, reveals that formation of the carbon skeleton by carbon-carbon bond forming reactions requires the most strategic planning. The largest number of actual chemical reactions in a synthesis, however, usually involves manipulation of functional groups (Smith, M. B. Organic Synthesis, McGraw-Hill, Inc. **1994**, Chapter 1). The functional group substitution from **X = NH or O** to **X = $S(O)_m$** changes the necessary starting materials for making these compounds as well as the predictability of their chemical reactivity. The functional group difference influences the bond length, electronegativity, and therefore the localization of electrons with respect to the functionality, which results in a lack of said predictability in their preparation. The art is silent with regard to the predictability of *any* compound as set forth by the formula (I) in with respect to its preparation, isolation, and use for treatments and a change in **X** would not only effect the chemical properties of the reagents for producing the desired

products, but inherently also effects the desired biological properties for this class of compounds. Therefore, it is unpredictable to know, from the outlined methods in the instant specification, how to make and use *all* of the compounds and/or physiological functional derivatives thereof as claimed in the formula (I).

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. There is a lack of information pertaining to the synthesis of formula (I) in which **X = $S(O)_m$** and examples that adequately represent this portion within the scope of the claimed invention. The examiner notes that the specification provides guidance to the invention only if **X = NH or O**, (specification, pages 24-54). The only guidance with respect to salts, solvates and derivatives of formula (I) are the definitions located on page 14 of the specification.

The existence of working examples

The working examples set forth in the instant specification are directed to the compounds of formula (I) for which **X = NH or O**. There has not been provided sufficient evidence that would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that *any* compound as claimed, specifically formula (I) wherein **X = $S(O)_m$,** would be able to be synthesized

using the methods outlined in Scheme 1. Furthermore, no examples have been presented for any salts, solvates and derivatives of a compound according to formula (I).

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

In view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of any compound of formula (I) as defined. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. Undue experimentation would include, for instance: the preparation of multiple synthetic outlines for each of the different definitions of **X**; the preparation of the necessary starting materials required for each of the compounds according to the formula (I) wherein $\mathbf{X = S(O)_m}$, followed by attempts to prepare a desired product for each of the different functional groups, subsequently followed by isolation, characterization, and testing the various compounds to determine if indeed they had utility for the treatment of various diseases.

The level of the skill in the art and the quantity of experimentation needed

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that discovering effective prodrugs is often underestimated and the process mimics the process conducted to discover the active

drug. Thus, the specification fails to provide sufficient support for the broad use of a prodrug of a compound according to formula (I).

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which prodrug design (functional group manipulation) will work for this class of compounds to determine if they would be encompassed in the instant claims, with no assurance of success. *This rejection can be overcome by deleting the unsupported language.*

Claims 38-40 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for the compounds and compositions described above and a method of using for the *treatment* of papovavirus, does not reasonably provide enablement for 1) the *prophylaxis* of papovavirus, or 2) the treatment or prophylaxis of all oncogenic viruses such as adenoviruses and retroviruses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of formula (I), the process for preparing these compounds, and methods of using these compounds.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for papovavirus, but it does not mean that the same group of compounds and compositions may prevent papovavirus. Furthermore, one of skill in the art would recognize that a family of compounds may treat papovavirus, bit it does not mean that the same family of compounds can treat other oncogenic viruses, such as adenoviruses and retroviruses.

Recently, the FDA approved Gardasil as the first prophylactic HPV vaccine. However, Gardasil contains recombinant virus-like particles assembled from the L1 (the HPV major capsid protein) proteins of HPVs 6, 11, 16 & 18. Gardasil is a non-analogous biotechnology with respect to the compounds according to formula (I), which are small molecule therapeutics.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the *prophylaxis* of papovavirus or for the treatment of other oncogenic viruses such as adenoviruses and retroviruses, as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of formula (I) to *treat* clinical conditions of HPV infection is found on pages 55 & 56.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 38-40 are drawn to "...use as medicament for the prophylaxis or treatment..." Prophylaxis is commonly known to be synonymous with prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Deleting the word "prophylaxis" in **Claims 38 & 39** as well as the non-enabled oncogenic viruses: adenoviruses and retroviruses, can overcome this rejection.

Claim Objections

Claims 2-25 & 28 are objected to as being dependent upon a rejected base **Claim 1**, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 15 is objected to because of the following informalities: "compound" is misspelled. Appropriate correction is required.

Claim 25 is objected to because of the following informalities: "pyridine" is misspelled on page 8/13, forth line from the bottom (contains the symbol □ instead of the letter p). Appropriate correction is required.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

REBECCA ANDERSON
PATENT EXAMINER

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

Joseph K. M^{c}Kane
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Date: February 26, 2007